

Author response:

## RESPONSE TO REVIEWERS

Reviewer: 1

### Comments to the Author

This is an appropriately designed study corroborating evidence for the efficacy and effectiveness of pirfenidone.

We would like to thank Reviewer 1 for your comment and for your precious advices that will help us to improve our paper.

I have only some minor comments:

1) You could expand a little the introduction section, which is short i.e. i suggest you to explain the reasons for increased morbidity ( the disease itself and commorbidities such as pulmonary hypertension and lung cancer). You could add a reference for these commorbidities. I would suggest that "Karampitsakos et al Pulm Pharmacol Ther. 2018 Pulmonary hypertension in patients with interstitial lung disease."

You may also use this reference as help for improvement of the introduction section "Fletcher et al Expert Opinion on Drug Safety 2016 The safety of new drug treatments for idiopathic pulmonary fibrosis"

1) We thank you for your suggestions. According to your advice, we enlarged the Introduction focusing on the comorbidities of IPF and the management of pirfenidone in clinical practice.

We have added the following sentences and references:

"The negative prognosis of IPF is related to the chronically progressive nature of disease, leading to a irreversible impairment of lung volumes and diffusion capacity, that results in respiratory failure development and to the exitus. Moreover, IPF is often complicated by many respiratory comorbidities, such as pulmonary hypertension, obstructive sleep apnea and lung cancer, that significantly worsen quality of life and life expectancy of these patients (6–8)."

Here we included the references you suggested.

2) Please rephrase the phrase "Morbidity and mortality are high, estimated 5-year survival being 20-40%" in the introduction section as there is a grammatical error.

2) Thank you for your reporting. We corrected the mistake.

3) introduction page 4 row 12: " an acceptable safety profile"

3) thank you for your reporting. We corrected the error as you suggested.

4) Discussion section is ver well written. I would just suggest further improving your concluding sentences by adding the words " Studies investigating effectiveness of pirfenidone in AE-IPF and studies investigating its synergistic effect with novel compounds that entered the pipeline of clinical trials (i.e. pamrevlumab, pentraxin) are greatly anticipated."

I would recommend that because data for effectiveness and safety are already known. The synergistic effect might be the hot topic of the upcoming years and if you mention that in your concluding sentences, then you enhance future perspectives of your manuscript. Towards this direction, you could add these 3 references in your concluding sentences.

1) Karampitsakos et al Front Med 2019 Biologic Treatments in Interstitial Lung Diseases

2)Raghu et al JAMA 2018 Effect of Recombinant Human Pentraxin 2 vs Placebo on Change in Forced Vital Capacity in Patients With Idiopathic Pulmonary Fibrosis: A Randomized Clinical Trial.

3) Richeldi et al Lancet RM 2019 Pamrevlumab, an anti-connective tissue growth factor therapy, for idiopathic pulmonary fibrosis (PRAISE): a phase 2, randomised, double-blind, placebo-controlled trial.

4) Thank you for your precious advice. We definitely agree with your assumptions on this field and we are happy to insert the following sentence and references in the Conclusion:

"Studies investigating effectiveness of pirfenidone in AE-IPF and studies investigating its synergistic effect with novel compounds that entered the pipeline of clinical trials (i.e. pamrevlumab, pentraxin) are greatly anticipated (27–29) and will hopefully transform the therapeutical management of patients."

Reviewer: 2

Comments to the Author

This is a retrospective single center review of patients with IPF treated with pirfenidone between 2011-2019. 91 patients are presented looking at the safety and efficacy of pirfenidone. The objectives of the study are clear. In that to explore long term efficacy and safety in a real world setting. Compared to other studies that have been published over the years on the real world safety of pirfenidone in IPF this study has a longer duration of follow up. 91 patients collected over a 8 year period spanning clinical trial, compassionate use and post authorisation (june 2013). This is a relatively small number of 11 patients per year. This study is not novel as there are other similar studies published of retrospective real world data n=12.

We would like to thank Reviewer 2 for the precious advices that will help us to improve our paper.

I enclose a number of comments that need addressing:

1. Abstract - Conclusion. Last sentence. I disagree with authors re further long term data required re pirfenidone. There are now numerous real world and post authorisation studies that confirm the safety and effectiveness of pirfenidone. So as a final sentence I would add that this study adds to the growing real world evidence to the safety and efficacy of pirfenidone in IPF.

1) Thank you for your suggestions. We agree that our study substantially confirmed previously published results, even though in a longer follow-up than other studies. Thus, following your advice, we replaced the last sentence of Abstract with the following phrase:

“This study, designed on a long-term follow-up, contributes to the growing evidence on safety, tolerability and efficacy of pirfenidone in IPF.”

2. Introduction line 12. References 6-8 are real world studies so I'd make it clear in this sentence that your statement is regarding real world studies. It makes logical sense to reference and discuss the clinical trial data before the open label extension studies and then the real world studies after these. This would make more chronological sense than the order at present which is ref 6-8 real world studies ref 9-10 clinical trials. 11-12 post authorisation studies and 13-14 real world data.

2. We thank you for your suggestion. Following your advice, we reorganized our introduction according to the chronological order suggested (clinical trials, post authorisation studies and real-world data).

3. Methods: clear. How often were lung function measurements taken?

3. Thank you for your reporting. Clinical assessment and PFTs are performed every 3 months in our Centre, except for specific clinical issues, including acute exacerbations of disease. We clarified this point in the Methods.

4. Results. Table 1 : I presume by Typical UIP you mean Definite UIP pattern. I would change this term to definite to be in line with ATS/ERS IPF guidelines

4. Thank you for your reporting. We corrected our mistake as you properly suggested

5, I would suggest a small paragraph summarising table 1 and 2 rather than just presenting the tables. Particularly with respect to your lung function findings

5. Thank you for your advice. As suggested, we summarised demographic and functional results with these following paragraphs:

“All 91 patients enrolled were included in the analysis of this study. As expected, most of our patients was male (78%), over 65 years old (72.5%), current/former smoker (63%) and reported at least one medical comorbidity. Exertional dyspnea and chronic dry cough were the main symptoms reported at onset. Baseline chest examination revealed bibasal crackles in all patients. The majority of patients showed a definite UIP pattern at high resolution computed tomography (HRCT) of the chest, while emphysema was radiologically evident in 15 patients (Table 1).

Concerning functional parameters, at baseline a mild restrictive impairment and a moderate reduction of DLCO was observed in our population. Beyond baseline assessment, PFTs were available in 40, 75, 51, 27 and 18 patients, at 12 months before recruitment and after 12, 24, 36 and 48 months of therapy, respectively (Table 2). “

6. Page 5 line 50. 10 patients switched from pirfenidone due to disease progression. How did you define progression. Please elaborate

6. Thank you for this comment, addressing a hot topic in the management of IPF treatment. In our clinical practice, we have always defined “functional progression” of IPF during the treatment as a 1-year decline of FVC > 10%, as suggested by Nathan et al. (Lancet Respir Med. 2017;5(1):33–41.) and clinical trials of pirfenidone and nintedanib. We understand that this cut-off may be misleading, as there is growing evidence demonstrating that pirfenidone and nintedanib probably prevent a even worse progression of disease and, thus, there would be no reasonable motivation to stop or switch antifibrotic therapy. However, this is a retrospective study focused on the routinary clinical practice of our Centre, that is a Regional Referral Centre for Interstitial Lung Disease and has participated to many RCTs for IPF. So, our “experience” with RCTs and post-hoc analysis may have influenced our clinical practice in the first years of antifibrotic therapy.

However, in order to clarify this point, we added the following sentence in Methods section:

“Functional disease progression was defined as a 1-year decrease of FVC > 10% and/or a 1-year decrease of DLCO > 15%, as previously suggested (19)”

7. Table 2. the mean FVC at pre treatment and baseline look similar yet the percentage FVC change at pretreatment is +6.6%. How is this the case. This is similar with the absolute values.

Similarly the FVC% looks similar at every time point post baseline yet the change in FVC% is very different. Please can this be explained

This is similar with DLCO results.

7. Thank you for your comment. This is one of the limitations of our study, due to its retrospective nature. Unfortunately, pretreatment PFTs were available only in 40/91 patients included in the study; thus, both percentage and absolute FVC changes reported in Table 2 are related to that specific subgroup of patients, while PFTs parameters reported in the Baseline column are related to all 91 patients. The same for all other parameters and columns of follow-up.

8. Discussion paragraph 2: May be worth describing the ml decline pre and post treatment.

8. Thank you for your advice. Following your suggestion, we included in that paragraph this data:

“(from  $210.5 \pm 251.4$  to  $91.7 \pm 237.4$  ml),”

9. discussion Page 8 Line 5. Term progressive increase in reduction is confusing please clarify/make clear

9. Thank you for your reporting. As suggested, we replaced the term increase with acceleration.

10. discussion page 8 Line 22. Cant say that pirfenidone prolonged life as no control. I would compare your survival to other published data.

10. Thank you for your reporting. Following your advice, we provided to re-write the cited paragraph, comparing indirectly our survival data with historical cohorts published in literature. Even indirectly, our data shows a substantial increase of survival time in respect to no-treatment cohorts, whose life expectancy has been estimated between 30-45 months. However, the improvement of survival with pirfenidone seems to be less significant compared to Fisher M et al. (J Manag Care Spec Pharm. 2017 Mar;23(3-b Suppl):S17-S24), Margaritopoulos et al (BMC Pulm Med. 2018; 18: 177.) and Zurkova et al. (Respir Res. 2019 Jan 21;20(1):16.). Unfortunately, many of these studies have been designed on post-hoc analysis of RCT trials, that excluded patients with major cardiovascular comorbidities or with advanced IPF. This aspect may overestimate the efficacy of pirfenidone in terms of survival by the exclusion of those patients with a higher risk of early death/referral to lung transplantation.

We address this issue with the following sentences in the discussion:

“Concerning mortality, our data showed a median survival of 1606 days. Despite the absence of a control group, if compared to other historical cohorts available in literature (14,18, 25), our data seems to confirm the efficacy of pirfenidone in prolonging life expectancy in IPF patients. However, the survival time of our population was worse than that reported in the Czech registry and RECAP study (12, 14). This discrepancy may be determined by inclusion in our study of a subgroup of patients with advanced IPF, who were taking pirfenidone on compassionate grounds”

11. General comments regarding discussion. Needs rewriting. No limitations discussed. Comment on the fact that HTN and GOR higher than registry data. 84% definite UIP high. Who looked at scans.. ?blinded. PFTs on 40 pre starting treatment limited numbers pre and post PFT data

Please explain drop out rates of patients at 12, 24, 36, 48 months. Not all due to deaths. Were patients lost to follow up. how does this affect your results. Side effects much lower than trials and other real world studies. needs discussion. AE-IPF 26% higher than trials discuss. Limitations not discussed; missing data ; retrospective nature potential bias.

11. Thank you for your comment that will help us to improve our paper. We agree with you regarding the limitations of our study and, thus, we added a paragraph addressing these critical issues of our paper. Unfortunately, retrospective nature of the study is prone to potential referral and reporting bias that cannot be totally eliminated. However, the main source of database comes from our clinical data, all collected in our Referral Centre for ILD. Undoubtedly, this aspect has helped to standardize the collection of clinical and functional data and allowed us to reduce the risk of reporting mistakes. Concerning comorbidities, both arterial hypertension and GOR prevalence is higher than data reported in clinical trials: this can be justified by the selection bias pursued in the inclusion criteria of RCTs. In fact, data on comorbidities from real-world setting is much more scattered and prevalence of hypertension and GERD is often reported as similar to our results (e.g.

Margaritopoulos et al. BMC Pulmonary Medicine (2018) 18:177). The high prevalence of comorbidities in our population may also be influenced by previous steroid therapy, particularly in those whose IPF diagnosis had been made before 2012 or those in compassionate use for pirfenidone. Moreover, our Centre protocol for IPF patients included a routine cardiological assessment at least yearly.

Concerning pattern UIP, as a Regional Referral Centre for IPF, we made diagnosis of IPF through multidisciplinary discussion since 2010. Thus, all data concerning CT scan has been retrospectively collected from MDDs. Both clinicians and radiologists are highly skilled in the diagnosis and management of interstitial lung disease and this aspect has been recently recognized by a WASOG award. The high prevalence of definite UIP in our cohort may be secondary to the strict Italian criteria for approving antifibrotic treatment in IPF patients, especially concerning pirfenidone. Many patients with probable or indeterminate UIP pattern were not allowed to start antifibrotic treatment, because of clinical, serological or BAL aspects that may rise the suspicion for secondary nature of ILD.

The high rate of drop-outs in the follow-up can be explained by clinical events (death, lung transplantation, interruption of treatment), incapacity to perform PFTs due to clinical conditions or to the shortness of observation (the last patient included had started pirfenidone at June 2017). Statistical analysis was conducted considering these patients lost to follow-up.

Regarding side effects, we are pretty sure about the incidence of hypertransaminasemia, that, according our Centre protocol, is regularly assessed every three months. On this issue, we reported in the manuscript only moderate to severe hypertransaminasemia: this could have underestimated the incidence of this side effect in our population. Concerning cutaneous and GI symptoms, the low incidence may be related to our preventing strategy, as already addressed in the Discussion

In our population, 25% of death was caused by acute exacerbation of IPF. The percentage value is due to the relatively low mortality in our population (30% of patients). Moreover, it seems difficult to compare our real-life study with clinical trials, planned with a different follow-up. RCT duration was approximately 12 months (vs our follow-up of more than 900 days, on average) and study protocols precluded the randomization of patients with advanced stage of disease. This aspect is surely relevant as AE-IPF is more common in patients with a severe impairment of lung volumes. Interestingly, post-hoc analysis (such as PASSPORT study) showed a higher incidence of AE than our population (20% vs 7%), although cause of deaths were not specifically addressed.

Finally, following your advices, we added these sentences in the Discussion:

“Concerning mortality, our data showed a median survival of 1606 days. Despite the absence of a control group, if compared to other historical cohorts available in literature (14,18,25), our data seems to confirm the efficacy of pirfenidone in prolonging life expectancy in IPF patients. However, the survival time of our population was worse than that reported in the Czech registry and RECAP study (12,14). This discrepancy may be determined by inclusion in our study of a subgroup of patients with advanced IPF, who were taking pirfenidone on compassionate grounds. In fact, other real-life studies (18,26) recruiting patients with severe disease, reported mortality data in line with ours. Moreover, our population showed a higher prevalence of medical comorbidities, such as arterial hypertension or gastroesophageal reflux disease, in respect to RCTs, RECAP and Czech registry studies (10–12,14), but comparable with other real-life studies (18). This data may be influenced by previous steroid therapy, particularly in those whose IPF diagnosis had been made before 2012 or those in compassionate use for pirfenidone.”

“We strongly encouraged use of sunscreens in all patients treated with pirfenidone and most patients were also on antiacid therapy. Moreover, as suggested by Costabel et al (28), patients were accurately informed concerning the potential adverse effects of pirfenidone and were strongly encouraged to apply the preventive measures suggested: these factors may have contributed to better tolerance of the drug.”

“Considering the aim of this research, our study is subject to many limitations: specifically, its retrospective and monocentric nature is typically prone to recall and/or misclassification bias. Moreover, the absence of a control group didn’t allow us a more precise evaluation of pirfenidone efficacy in reducing the progression rate of disease.”

“Studies investigating effectiveness of pirfenidone in AE-IPF and studies investigating its synergistic effect with novel compounds that entered the pipeline of clinical trials (i.e. pamrevlumab, pentraxin) are greatly anticipated (28–30) and will hopefully transform the therapeutical management of patients.”

12. Figure 1. Please put statistical results on graph figure and improve legend by explaining the stats

12. Thank you for your comment. We improved Figure 1 putting statistical remarks on the graph and explaining them in the related figure caption.

13. Figure 3. Not sure if it adds anything to the text. consider removing

13. Thank you for your advice. After collegial decision, we removed the figure.